The paragraph bridging pages 6 and 7 of the instant specification teaches that Gross et al. relate to molecules that are constructed using the α and β chains of the Ti portion of the T cell receptor. Ti is composed of the α and β chains, page 6, lines 24 and 25 of the instant specification. The Ti chains bind antigen but do not have innate signaling capacity (lines 29-32 on page 6 of the instant specification). Instead, the α and β chains interact with the CD3/ζ chains present in another part of the T cell receptor complex, lines 32 and 33 on page 6 of the instant specification, and as uncovered in the instant invention, the ζ chains initiate the intracellular signal. The Gross et al. receptors, like the native α and β chains, do not possess innate signaling capacity (lines 4-7 on page 7 of the instant specification).

The Examiner indicated that Gross et al. express the receptor in cytotoxic T cell hybridomas that appear to contain endogenous wild-type T cell receptors. Gross et al. teach in the second to the last sentence in the Abstract that the chimeric chains pair with endogenous β or α chains of the host T cell. That can be seen also in the data of, for example, Figure 3 and Table 1 of Gross et al. The control samples revealed that the host T cell hybridoma, MD.45, a cell line that reacts to the H-2^b haplotype, responds to the EL4 cell which is a C57BL/6 lymphoma with the H-2^b haplotype (page 10027, left column, lines 5 and 6 of Gross et al.). The Gross et al. host cell, without a chimeric receptor, responds to antigen and thus, must express a functional T cell receptor.

Therefore, the Gross et al. receptors cannot signal in the absence of T cell receptor. Accordingly, the instant invention is not anticipated by Gross et al.

II. In item 5 on page 3 of the Office Action, Applicants thank the Examiner for acknowledging the patentability of claim 59. However, as will be explained in greater detail

hereinbelow, claim 59 need not be written in independent form because claim 57 on which claim 59 depends also is patentable.

III. In item 8 bridging pages 3 and 4 of the Office Action, claims 57, 64, 65, 67 and 71 were rejected under 35 U.S.C. § 112, first paragraph. The issue was one of new matter.

The rejection is traversed for the following reasons.

As discussed in part hereinabove, Gross et al. do not teach a chimera that can signal in the absence of a T cell receptor. The instant invention is directed to chimeric proteins that contain cytoplasmic domains capable of autonomously signaling in the absence of a T cell receptor. As provided in the Summary of the Invention on page 7 of the instant specification, lines 24-27, particular cytoplasmic sequences comprise the novel chimeric molecules of the instant invention.

To demonstrate that the chimeric molecules of interest can signal autonomously in the absence of an intact T cell receptor, a chimeric receptor was expressed in a host cell that does not express T cell receptor. As taught at lines 27-32 of page 30 of the instant specification, an exemplary chimeric construct was transfected into two cell lines, Jurkat, a human T cell leukemia that expresses T cell receptor, and **a mutant of Jurkat, JRT3.T3.5, that does not express T cell receptor**, see particularly lines 1-7 on page 31 of the instant specification.

The normal Jurkat cell that expressed an exemplary chimeric receptor of interest was identified as JCD8/ζ2 (page 30, line 30 of the instant specification), whereas the Jurkat

mutant clone deficient in T cell receptor that expressed a chimeric receptor of interest was known as Jβ-CD8/ζ14 (page 30, line 32 of the instant specification).

The two cell lines were tested in a variety of ways to determine if the chimeric receptors of interest could signal, and signal in the absence of a T cell receptor, see pages 33-38 of the instant application. For example, stimulation of the chimeric molecule in the two cell lines with an antibody directed to the extracellular domain of the receptor, CD8, resulted in appearance of phosphorylated protein bands indistinguishable from that seen with T cell receptor stimulation (lines 11-20 on page 35 of the instant specification).

Example 5 of the instant specification teaches construction of other chimeric receptors of interest using claimed cytoplasmic domains. The second full paragraph on page 4 of the instant specification teaches that the η chain is an alternatively spliced product of the same gene that yields the ζ chain. Tyrosine kinases are taught in the paragraph bridging pages 5 and 6 of the instant specification. The Examiner acknowledged the patentability of the γ chain of the F_c receptor.

Clearly, the chimeric molecules of interest activate cells in the absence of T cell receptor.

Accordingly, the instant application fully teaches and supports chimeric receptors that signal in the absence of a T cell receptor. No issue of new matter exists and the claimed invention is in full compliance with 35 U.S.C. § 112, first paragraph.

In view thereof, withdrawal of the rejection is in order.

IV. In item number 9 on page 4 of the Office Action, claims 57, 64, 67, 69 and 71 were rejected under 35 U.S.C. § 102(b) over Kuwana et al.

The rejection is traversed for the following reasons.

As noted in the Summary of Kuwana et al., page 960 thereof, the receptors taught therein comprise the α and β genes. Hence, the receptors of Kuwana et al. are of the same type as that of Gross et al. and it is known that α and β chains do not signal autonomously.

Moreover, the host cells of Kuwana et al., EL4 cells, express T cell receptor. For example, as noted in Goverman et al., Cell 60:929-939, 1990, copy attached hereto for the convenience of the Examiner, page 930, right column, line 4-up, Goverman et al. teach that EL4 expresses T cell receptor.

Hence, Kuwana et al. do not teach a chimeric receptor that can signal in the absence of intact T cell receptor. The α and β chains do not signal in the absence of a T cell receptor. The host cell of Kuwana et al. expresses intact T cell receptor. In view thereof, Kuwana et al. do not anticipate the instant invention and withdrawal of the rejection is in order.

V. In item 10 on page 5 of the Office Action, claims 57, 64, 67, 69 and 71 were rejected under 35 U.S.C. § 102(e) over Eshhar et al.

The rejection is traversed for the following reasons.

Eshhar et al. is cumulative to Gross et al. in teaching chimeric receptors comprising the α and β chains. Thus, for the same reasons with respect to Gross et al. and Kuwana et al., Eshhar et al. do not teach a chimeric receptor that signals in the absence of T cell receptor.

As taught in Eshhar et al., host cells include the MD.45 cell and Jurkat cells, both of which express T cell receptor. As noted in the paragraph bridging columns 3 and 4 of Eshhar et al., the only cells that can be used as hosts of the Eshhar et al. chimeric receptors are those that express T cell receptor, particularly lines 65 and 66 in column 3 of Eshhar et al.

Finally, the Examiner noted that Eshhar et al. relate to α, β, γ and δ chains. However, the γ and δ chains of Eshhar et al. are not the CD3 γ and δ chains of the instant invention.

Eshhar et al. take molecules having an immunoglobulin-like structure containing a variable region and a constant region and rearrange homologous segments from those molecules. The result is a molecule with a variable region and a constant region of different origins (column 4 of Eshhar et al., lines 15-23).

Goverman et al., page 929, right column, first full paragraph, lines 15-23, teach that a small number of Ti molecules associated with CD3 are composed of a γ and a δ chain, which are similar to α and β chains.

Weiss, Journal of Clinical Investigation 86:1015-1022, 1990, of record, copy submitted with the Amendment filed 8 March 1999 and another copy attached hereto for the convenience of the Examiner, in Figure 1, teaches the basic configuration of the T cell receptor complex comprising Ti, having the α and β chains, and the CD3 complex, containing the γ, δ, ε and ζ chains. As noted on page 1016, right column, third full paragraph of Weiss, a certain number T cells contain a Ti complex comprising a γ and a δ chain associated with the CD3 complex. The γ and δ chains are similar to the α and β chains.

On the other hand, the instant invention relates to the γ and δ chains of the CD3 complex. These molecules do not have an immunoglobulin-like structure.

Clearly, the γ and δ chains of Eshhar et al. are those with an immunoglobulin-like structure and are similar in structure to the α and β chains, as compared to the γ and δ chains of the CD3 complex. The γ and δ chains of the CD3 complex are those of the instant invention.

Hence, Eshhar et al. do not teach the instant invention and the rejection can be removed.

CONCLUSION

Applicants thank the Examiner for his guidance. In view thereof and in view of the instant Amendment, reexamination, reconsideration, withdrawal of the rejections and early indication of allowance are solicited earnestly. If any issues remain unresolved, the Examiner can contact the undersigned at the local exchange noted hereinbelow.

The Commissioner hereby is authorized to charge or to credit any shortage or overage to Deposit Account No. 18-2220.

Respectfully submitted,

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Dated: 4 April 2001

AMENDMENT UNDER 37 C.F.R. § 1.116
EXPEDITED PROCEDURE
GROUP 1600
PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of

Capon et al.

Appln. No.: 08/238,405 Group Art Unit: 1645

Filed: 5 May 1994 Examiner: R. Hayes

For: CHIMERIC CHAINS FOR RECEPTOR-ASSOCIATED SIGNAL TRANSDUCTION PATHWAYS

AMENDMENT UNDER 37 C.F.R. § 1.116

ATTN: BOX AF
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

This Amendment is responsive to the Final Office Action mailed 26 May 1999 and the Notice of Appeal filed 24 November 1999.

Kindly amend the application as follows.

IN THE CLAIMS:

Amended 5-1-01

57. (A ~~Fourth~~ Time) A chimeric protein comprising in the N-terminal to C-terminal direction:

an extracellular antigen-binding domain of a single chain antibody that binds specifically to an antigen, wherein said antigen is a protein on the surface of a cell or a viral protein;

a transmembrane domain; and

a cytoplasmic domain which transduces a signal resulting in activation of a secondary messenger system in the absence of a T-cell receptor, and when said chimeric protein is expressed as a membrane bound protein in a selected mammalian host cell under conditions suitable for expression, said membrane bound protein initiates signaling in said host cell when said extracellular domain binds to said antigen. (wherein said cytoplasmic domain is selected ... claim 71)

69. (Twice Amended) The mammalian cell of Claim 64 wherein said cell is [substantially free of surface expression of at least one of the Class I or Class II Major Histocompatibility Complex antigens] not recognized as foreign in a host.

REMARKS

As noted at pages 30-33 and at page 36 of the instant application, the instant receptors autonomously signal in the absence of T cell receptor.

As taught at page 22, lines 10-16 of the instant application, a cell can be manipulated so as not to be recognized as foreign when placed in a host.

As no issue of new matter is raised by the above amendments, entry thereof is requested respectfully.

67. (Amended) [A] The mammalian cell [comprising as a surface membrane protein, a protein according to] of Claim [82, wherein said cell] 64, which is a cytotoxic T lymphocyte.

69. (Twice Amended) [A] The mammalian cell [comprising as a surface membrane protein, a protein according to] of Claim [85] 64 wherein said cell is substantially free of surface expression of at least one of Class I or Class II Major Histocompatibility Complex antigens.

Kindly add the following new claim 71.

Cancel --71. A protein according to claim 57, wherein said cytoplasmic domain is selected from the group consisting of the CD3 zeta chain, the CD3 eta chain, the CD3 gamma chain, the CD3 delta chain, the CD3 epsilon chain, the gamma chain of F_c receptor and a tyrosine kinase.--

REMARKS

I. A substitute Declaration relating to co-inventor Irving will be filed shortly.